METHOD AND APPARATUS FOR CELL AND ELECTRICAL THERAPY OF LIVING TISSUE

Cross-Reference to Related Application(s)

This application claims the benefit of U.S. Provisional Application No. 60/429,954, filed on November 30, 2002, under 35 U.S.C. § 119(e), which is hereby incorporated by reference.

This application is related to co-pending, commonly assigned U.S. Patent Application Serial No. _____, "METHOD AND APPARATUS FOR CELL AND ELECTRICAL THERAPY OF LIVING TISSUE," filed on November 25, 2003 (Attorney Docket No. 279.597US1), which is hereby incorporated by reference.

Technical Field

This invention relates generally to combined cell and electrical therapy of living tissue and particularly, but not by way of limitation, to method and apparatus for conditioning living tissue using cell and electrical therapy with a cardiac rhythm management system.

Background

The heart is a unique organ which pumps blood not only to the remaining portions of the body, but to itself. "Heart attacks" or myocardial infarctions occur when there is a loss of proper blood flow to the heart. When heart tissue does not get adequate oxygen, there is a high probability that heart muscle cells will die. The severity of a heart attack is measured by the amount and severity of heart damage.

Heart disease is a leading cause of death. Despite advances in the treatment of heart attacks, patients suffer decreased quality of life due to the damage caused by the heart attack. One such damage is chronic heart failure arising from the heart attack. The cardiac muscle cells, cardiomyocytes, which, in some circumstances, die during a heart attack either cannot be regenerated naturally by the heart or cannot be regenerated in sufficient quantities to repair the damage following a heart attack.

Depending on the severity of damage to the heart muscle, cardiac output, heart value function, and blood pressure generating capacity can be greatly reduced. These results only exemplify some of the long-term devastating impacts of heart attacks on patients.

One way to treat damaged heart muscle cells is to provide pharmaceutical therapies in an effort to restore heart function. Such therapies may not be particularly effective if the damage to the heart is too severe, and pharmaceutical therapy is not believed to regenerate cardiomyocytes, but instead acts to block or promote certain molecular pathways that are thought to be associated with the progression of heart disease to heart failure.

Another treatment for damaged heart muscle cells is called "cell therapy." Cell therapy involves the administration of endogenous, autologous and/or or nonautologous cells to a patient. For example, myogenic cells can be injected into damaged cardiac tissue with the intent of replacing damaged heart muscle or improving the mechanical properties of the damaged region. However, the administration of myogenic cells does not ensure that the cells will engraft or survive, much less function and there is a need in the art for enhanced efficacy of cell therapies.

Summary

This document discloses, among other things, a method and apparatus for synergistic actions among cell and electrical therapies of living tissue.

In varying embodiments, a system for electrical therapy of cardiac tissue of a heart, at least a portion of the cardiac tissue administered with exogenous cells in a cell therapy, including one or more catheter leads with electrodes; a pulse generator comprising an interface for connection to the one or more catheter leads, a controller programmable for a plurality of pulse delivery modes, and a sense amplifier for sensing electrical signals from the one or more catheter leads; and wherein the pulse generator includes a selectable pacing mode for providing therapeutic electrical stimulation to enhance the cell therapy of the cardiac tissue.

In various embodiments, the therapeutic electrical stimulation includes a VDD pacing mode having an atrioventricular delay which is short compared to an intrinsic atrioventricular delay of the heart.

Also described are embodiments where the therapeutic electrical stimulation is provided at times between additional pacing and defibrillation therapies, where the therapeutic electrical stimulation is programmable for certain times of day, such as for sleep times.

Also described are embodiments where the therapeutic electrical stimulation is programmable for certain levels of stress, or for certain levels of activity.

A variety of embodiments are provided where the therapy is invoked by a programmer, where accelerometer data is used to determine when to apply therapeutic electrical stimulation and where lead location is used to determine types of therapeutic electrical stimulation, for some examples.

Also discussed are methods for enhancing cell therapy of cardiac tissue including applying electrical therapy using an implantable pulse generator to cardiac tissue administered with exogenous cell therapy comprising donor cells, wherein the electrical therapy enhances one or more of engraftment, survival, proliferation, differentiation or function of the donor cells. Different methods including *in vivo* and *in vitro* treatments are discussed. Various pacing therapies are also discussed. In one embodiment, the methods include administering an agent that enhances exogenous cell engraftment, survival, proliferation, differentiation, or function. Enhancement of cardiac function and angiogenesis are also discussed.

The description also provides various catheters for cell therapy, including needle means for injection of fluids for cell therapy.

This Summary is an overview of some of the teachings of the present application and not intended to be an exclusive or exhaustive treatment of the present subject matter. Further details about the present subject matter are found in the detailed description and appended claims. Other aspects of the invention will be apparent to persons skilled in the art upon reading and understanding the following detailed description and viewing the drawings that form a part thereof, each of which

are not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims and their equivalents.

Brief Description Of The Drawings

In the drawings, like numerals describe similar components throughout the several views. Like numerals having different letter suffixes represent different instances of the components.

FIG. 1A is a flow diagram showing an overall therapy using cell therapy and electrical therapy according to one embodiment of the present invention.

FIG. 1B is a flow diagram showing a particular therapy for treating cardiac tissue using combined cell and electrical therapies according to one embodiment of the present invention.

FIG. 2A is a drawing of a side view of a catheter tip for providing cell therapy according to one embodiment of the present invention.

FIG. 2B is a drawing of a top view of a catheter tip for providing cell therapy according to one embodiment of the present invention.

FIG. 2C is a side view of one embodiment of a catheter tip with adjustable curvature according to one embodiment of the present invention.

FIG. 2D is a drawing of a side view of a catheter tip with separate channels for vacuum and needle for providing cell therapy according to one embodiment of the present invention.

FIG. 2E is a drawing of a side view of a catheter tip with drug reservoir and electrodes for providing cell therapy according to one embodiment of the present invention.

FIG. 2F is a drawing of a catheter tip having a needle array for providing cell therapy according to one embodiment of the present invention.

FIG. 2G is a drawing of the catheter tip of FIG. 2F with the needle array retracted and tissue after cell therapy according to one application of the present invention.

FIG. 2H is a drawing of a catheter tip with expandable balloon for cell therapy according to one embodiment of the present invention.

FIG. 3 is a block diagram of a pacemaker according to one embodiment of the present invention.

FIG. 4 shows one example of application of cell and electrical therapy to a region of cardiac tissue subject to myocardial infarction according to one embodiment of the present invention.

FIG. 5A is a diagram showing a programmer for use with an implanted cardiac rhythm management device according to one embodiment of the present invention.

FIG. 5B is a diagram showing a wireless device in communications with an implanted device for management of the implanted device and therapy according to one embodiment of the present invention.

FIG. 5C is a diagram showing a wireless device in communications with an implanted device and connected to a network for communications with a remote facility for management of the implanted device and therapy according to one embodiment of the present invention.

Detailed Description

In the following detailed description, reference is made to the accompanying drawings which form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that the embodiments may be combined, or that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the spirit and scope of the present invention. The following detailed description provides examples, and the scope of the present invention is defined by the appended claims and their equivalents.

It should be noted that references to "an", "one", or "various" embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment.

General Overview

This document describes, among other things, method and apparatus for cell therapy and electrical conditioning of living tissue. In one embodiment, cell therapy is applied to tissue *in vivo* by locating damaged tissue and administering, e.g., inserting or applying, appropriate cellular material ("donor cells") into and/or to the damaged tissue. In one embodiment, the area including the damaged tissue and donor cells are then subjected to electric conditioning, such as pacing-level electrical stimulation, using a pulse generator with properly positioned electrodes. Several embodiments are presented below to provide examples of different therapy apparatus and method. It is understood that other apparatus and method are possible as provided by the attached claims and their equivalents.

FIG. 1A shows a flow chart for providing combined cell and electrical therapy according to one embodiment of the present invention. A region of the tissue to be treated is identified 100. Cell therapy is administered to the identified region 110. Electrical therapy is applied to the identified region 120. In one approach, the cells ("donor" cells) are administered concurrently with electrical therapy, while in other approaches electrical therapy is subsequent to cell administration. In another approach electrical therapy is applied prior to cell administration. Moreover, it is understood that multiple cell therapies may be implemented prior to application of the electrical therapy to the identified tissue region. Also for example, the cell therapy may be followed by multiple electrical therapies. It is understood that different permutations of cell and electrical therapy may be performed in varying embodiments. For instance, electrical conditioning may be applied before, during, or after cell therapy. In one approach cellular engraftment, cellular proliferation, cellular differentiation, cellular survival and/or cellular function, e.g., contractile function, of the donor cells in the recipient is further enhanced by electrical stimulus from the electrical therapy.

In one embodiment an advanced patient management device is used to control the applied electrical therapy in conjunction with inputs regarding applied cell therapy, inputs regarding patient health, and inputs regarding environmental conditions. Other inputs are contemplated, and those provided herein are intended to demonstrate the

flexibility and programmability afforded the user when the cell and electrical therapies are managed with an advanced patient management system. Such a system is discussed in various applications by the assignee, including, but not limited to, in U.S. Patent Application Ser. No. 10/093,353, filed March 6, 2002, which is hereby incorporated by reference in its entirety.

Example of Cell Therapy of Cardiac Tissue

The present teachings are useful in a number of therapies. In one example, the treatment of a failing heart is possible. Such therapies may be employed for both ischemic and non-ischemic heart failure etiologies. In one example application where the damaged tissue to be treated is cardiac tissue, the cardiac tissue region (or regions) of damaged tissue are identified 130 and then cell therapy is administered to one or more areas of damaged tissue 140. Tissue damage resulting from a myocardial infarction or heart attack is one type of tissue treatable by these apparatus and methods.

Different methods of locating the damaged tissue may be employed. For example, electrophysiology, such as electrocardiograms, can be used to locate damaged cardiac tissue. Other locating methods include, but are not limited to: echocardiography and catheter-based voltage mapping of a portion of the heart; catheter based strain mapping; invasive or minimally invasive surgery (visualization of damaged tissue); and other imaging techniques, such as MRI, perfusion imaging, fluoroscopy, and angiography.

Once the damaged tissue is located, the localized area may be treated by inserting or applying donor cells, e.g., cells administered intravenously, transvenously, intramyocardially or by any other convenient route, and delivered by a needle, catheter, e.g., a catheter which includes an injection needle or infusion port, or other suitable device. Some exemplary delivery apparatus and methods include, but are not limited to, the teachings provided in the patent applications entitled: Drug Delivery Catheter with Retractable Needle, U.S. Ser. No. 09/746,498 filed December 21, 2000; and Intra-Ventricular Substance Delivery Catheter System, U.S. Ser. No. 10/038,788,

filed December 31, 2001. Both of these disclosures are incorporated by reference in their entirety.

In one embodiment, a catheter having a catheter tip 200 adapted for injection of exogenous cellular material is used for cell therapy. FIG 2A shows a side view of a catheter tip 200 positioned near the myocardium 202 having damaged cardiac muscle tissue. The catheter tip 200 is positioned intrapericardially intravenously, transvenously, transarterially, intramyocardially, or by another method. A suction port 208 is shown from a top view in FIG. 2B at the distal end of the catheter. The catheter tip 200 is affixed near the region to be treated by a vacuum applied at the proximal end of the catheter to create a vacuum at the suction port 208 via channel 206 and thereby hold the catheter tip 200 against the myocardium 202. A hollow needle 204 is then advanced into the tissue at the catheter tip to inject exogenous cellular material to the location for cell therapy. After injection is complete, the hollow needle 204 is retracted into catheter tip 200 and the vacuum is removed so that the catheter tip 200 can be repositioned for therapy at a different location.

In one embodiment, the needle is deployed through a channel and and using an actuator at the proximal end of the catheter. In the example where a common channel is used between the vacuum and the needle, the vacuum channel is sealed where the needle exits the catheter at the proximal end to maintain any vacuum applied to the channel. The hollow needle in this embodiment uses a conduit from the proximal end to the distal end of the catheter. In one embodiment, injection of fluid is accomplished using a luer fitting and needle at the proximal end. Manipulation of the needle is accomplished using the actuator at the proximal end of the catheter.

The example demonstrated in FIG. 2A employs channel 206 for both the application of vacuum and a means for guiding hollow needle 204 and storing it when it is retracted. Other embodiments are provided herein where the suction port and needle use separate channels. For example, FIG. 2D shows a catheter tip 216 having suction port 218 with channel 220 and a hollow needle 222 with channel 224. In this example embodiment, channel 220 and channel 224 are separate. Other configurations are possible without departing from the scope of the present teachings.

In the embodiment with separate channels, a separate fitting for the vacuum and for the needle are used to apply the vacuum and inject fluid, respectively. In on embodiment a standard luer fitting is used and needle is used to inject the fluid.

FIG. 2C shows one example of an embodiment where the catheter tip 210 is able to achieve an angle of curvature to provide a surface that conforms to a portion of a curved myocardium. In one embodiment, the angle of curvature is approximately 30 degrees. In varying embodiments the tip may be adjusted to perform differing degrees of deflection to adjustably position the suction port near the location to be treated. In one embodiment, the adjustment is performed using a stylet inserted into a pre-bent catheter tip portion. FIG. 2C demonstrates this by including a stylet channel 212 which accommodates stylet 214 in varying positions to show that as the stylet is removed, the angle of the tip changes and is thus adjustable. Other adjustment techniques may be employed without departing from the scope of the present teachings.

FIG. 2E shows one embodiment of the catheter tip 226 where the tip is includes one or more contacts 228 connected to the proximal end and a drug reservoir 230 with elution means to perform iontophoresis. Various locations of possible electrode positions are demonstrated in FIG. 2E. In one embodiment, a chemical reservoir is included at the catheter tip for iontophoretic transfer into the adjacent tissue. In one embodiment, a porous electrode is used to transfer fluid from the catheter tip.

In varying embodiments, the catheter is dimensioned for different sizes to facilitate transvenous positioning of the cathode tip. In one embodiment, the catheter is available in diameters varying from 10 French to 24 French. Other sizes are possible without departing from the present teachings.

Another embodiment of a catheter tip for injection of exogenous cells is shown in FIG. 2F. In this example, the catheter tip 232 includes a needle array 236 which provides a plurality of needle points for injection into tissue 234. The needle array provides multiple pathways for delivery of material and lower delivery resistance.

The catheter tip 232 also includes fiber optic 238 for visualizing the region and locating the catheter tip 232 for treating tissue 234.

In one embodiment, the needle array 236 is retractable for ease of transvenous and transarterial delivery. In one embodiment, the needle array 236 includes needle points that are approximately 0.5 cm in length. In varying embodiments, the needle array includes needles of varying lengths to provide a contour of tip points. In varying embodiments the needle array provides 2 - 3 mm of penetration into tissue. Other embodiments are possible without departing from the scope of the present teachings.

In one application demonstrated by FIG. 2G, a plurality of columns 244 of material are injected into tissue 242 by catheter tip 240. (The catheter tip 240 is shown in a retracted mode in FIG. 2G.) The columns 244 may contain cellular material and/or drugs and serve as passive molecule factories in tissue 242.

It is understood that the number and placement of tines may vary. Diameters and distances provided herein are intended to provide nonexclusive examples and are not intended in an exclusive or limiting sense.

Another embodiment of a catheter-based delivery system includes the use of a balloon and delivery catheter. FIG. 2H shows one example of a catheter tip 250 which is insertable transvenously and transarterially for the delivery of cellular materials to a vessel or organ. Catheter tip 250 includes balloon 252 for occluding the lumen 248 and providing a temporary blockage for the material 254 to remain in space 256 for a period of time. Space 256 is treated with the cellular material, and then balloon 252 is deflated for withdrawal of the catheter tip 250.

It is understood that various combinations of the examples provided above are possible. For example, a fiber optic may be used to place the catheter tip and may be combined with the catheter tips having common and independent channels for the vacuum and the needle and or needle array. Other combinations are possible without departing from the scope of the present teachings.

Combined cell and electrical therapy may also be accompanied by the administration of drugs to the recipient animal.

Variations in design and placement of elements may be implemented without departing from the teachings provided herein, and the examples given are not intended in a limited or exclusive sense.

Sources of Donor Cells for Cell-Based Therapies

Sources for donor cells in cell-based therapies include skeletal muscle derived cells, for instance, skeletal muscle cells and skeletal myoblasts; cardiac derived cells, myocytes, e.g., ventricular myocytes, atrial myocytes, SA nodal myocytes, AV nodal myocytes, and Purkinje cells; bone marrow-derived cells, e.g., mesenchymal cells and stromal cells; smooth muscle cells; fibroblasts; or pluripotent cells or totipotent cells, e.g., teratoma cells, hematopoietic stem cells, for instance, cells from cord blood and isolated $CD34^+$ cells, multipotent adult progenitor cells, adult stem cells and embyronic stem cells. In one embodiment, the donor cells are autologous cells including xenologous cells, however, non-autologous cells may be employed. The donor cells can be expanded *in vitro* to provide an expanded population of donor cells for administration to a recipient animal. In addition, donor cells may be treated *in vitro* to cause a preferred differentiation. Sources of donor cells and methods of culturing those cells are known to the art. See, for example, U.S. Patent No. 5,130,141 and Jain et al. (Circulation, 103, 1920 (2001)), wherein the isolation and expansion of myoblasts from skeletal leg muscle is discussed (see also Suzuki et al., Circulation, 104, I-207 (2001), Douz et al., Circulation, III-210 (2000) and Zimmerman et al., Circulation Res., 90, 223 (2002)). Published U.S. Application 20020110910 discusses the isolation of and media for long term survival of cardiomyocytes. U.S. Patent No. 5,580,779 discusses isolating myocardial cells from human atria and ventricles and inducing the proliferation of those myocardial cells. U.S. Patent No. 5,103,821 discusses isolating and culturing SA node cells. For SA node cells, the cells may be co-cultured with stem cells or other undifferentiated cells. U.S. Patent No. 5,543,318 discusses isolating and culturing human atrial myocytes. U.S. Patent Nos. 6,090,622 and 6,245,566 discusses preparation of embryonic stem cells, while U.S. Patent No. 5,486,359 discusses preparation of mesenchymal cells.

The donor cells may also be manipulated *in vitro* to introduce one or more desirable gene products (transgenes) to the cells. Preferably, the transgenic donor cells include a transgene that enhances cellular proliferation, cellular engraftment, cellular survival, cellular differentiation and/or cellular function of the donor cells in the recipient. The expression of one or more transgenes may be employed to decrease, replace or supplement (increase) the expression of endogenous genes in the donor cells, e.g., if the donor cells are autologous cells and the donor has an inherited or acquired disease associated with aberrant expression of an endogenous gene in cardiac cells. The expression of one or more transgenes may correct the level of the gene product encoded by the transgene in the donor cells. In one embodiment the expression of the transgene is controlled by a regulatable or tissue-specific, e.g., cardiac myocyte-specific promoter. The transgene may be introduced to donor cells by any means including but not limited to liposomes, electroporation, naked DNA, or viral-mediated transduction, for instance, via adenovirus, adeno-associated virus, retrovirus or lentivirus vectors.

Compositions, Dosages and Routes of Administration of the Donor Cells

Compositions of the invention comprise donor cells, including cells from different sources, and optionally agents that enhance donor cell engraftment, survival, proliferation and/or differentiation, enhance cardiac function or stimulate angiogenesis. The cells to be administered may be a population of individual cells or cells grown in culture so as to form a two dimensional or three dimensional structure. The number of cells to be administered will be an amount which results in a beneficial effect to the recipient. For example, from 10^2 to 10^{10}, e.g., from 10^3 to 10^9, 10^4 to 10^8, or 10^5 to 10^7, cells can be administered to, e.g., injected, the region of interest, for instance, infarcted and tissue surrounding infarcted tissue. Agents which may enhance cardiac function or stimulate angiogenesis include but are not limited to pyruvate, catecholamine stimulating agents, fibroblast growth factor, e.g., basic fibroblast growth factor, acidic fibroblast growth factor, fibroblast growth factor-4 and fibroblast growth factor-5, epidermal growth factor, platelet-derived growth factor, vascular

endothelial growth factor (e.g., $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{189}$ or $VEGF_{206}$), tissue growth factors and the like. Such agents may optionally be present in the compositions of the invention or administered separately.

The cells are administered during a prophylactic, diagnostic or therapeutic vascular procedure or an invasive or minimally invasive surgical procedure. In one embodiment, the cells are administered post-MI, within hours, e.g., 1 to 12 hours, to days, e.g., 1 to 2 days, and up to one or more weeks after MI. Preferably, the administration of donor cells is prior to scar formation. The cells may be administered intravenously, transvenously, intramyocardially or by any other convenient route, and delivered by a needle, catheter, e.g., a catheter which includes an injection needle or infusion port, or other suitable device. Some exemplary delivery apparatus and methods include, but are not limited to, the teachings provided herein.

In one embodiment, once administered, the donor cells develop functional connections with adjacent cells, membrane channels with adjacent cells, including viable cells in the recipient, and, if not already differentiated, differentiate to myocardial cells.

Example of Electrical Therapy of Cardiac Tissue

Following cell therapy, the identified region of tissue to be treated is subjected to electrical therapy 150. In the example of cardiac tissue, electric current is imposed across or adjacent to the damaged tissue. In one embodiment a pacemaker with implanted catheter leads is employed to provide the appropriate pacing stimulation to the identified region of tissue. In varying embodiments, one or more electrodes serve to apply an electric field over portions of the identified tissue region. In implanted pacemaker applications the pacemaker housing may serve as an electrode.

In one embodiment, the pacemaker is programmed to perform VDD pacing using an atrioventricular delay which is relatively short when compared to the intrinsic atrioventricular interval. In such embodiments, the electrical pace wavefront is near the infarcted region very early in the cardiac cycle so as to electrophysiologically capture and mechanically unload the identified region with the pacing stimulus. The

VDD mode of the pacemaker allows the heart to maintain a rate near to that of a normal sinus rhythm, providing better control of the activation pattern; the ventricles are pre-excited without advancing the pacing rate unnecessarily. In this way, the depolarization wavefront fuses with the paced complex, resulting in the most intrinsic activation of the ventricles, yet providing for the pre-excitement of the damaged tissue region. Other pacing modes are possible, and those provided here are not intended in an exhaustive or exclusive sense.

In varying embodiments and combinations, the electrical therapy includes different programming modes for use with a particular cell therapy. In one embodiment, electrical therapy is invoked during periods of relative inactivity such as are common during nocturnal sleep to condition the cardiac tissue and improve cell engraftment. In one embodiment, electrical therapy is invoked based on physical activity of the patient during which heart wall stress is reduced via electrical pre-excitation. Such physical activity may be measured by detection of accelerometer data. In one embodiment, the electrical therapy is invoked for certain times of day or during specifically programmed, recurring patterns of intrinsic (M beats) and paced beats (N beats) in a ratio of M:N. In embodiments featuring programmable microprocessors, the time of day is downloaded to the microprocessor upon programming and therapy is programmably selectable. In varying embodiments and combinations, electrical therapy is delivered upon preselected sensor inputs. For example, electrical therapy is invoked (continuous or M:N patterns) upon detected patient activity. In one embodiment, electrical therapy is invoked upon detection of patient stress. In one embodiment, electrical therapy is invoked upon detection of patient metabolic high stress in the heart, such as in sleep, where ventricles are distended and filling better. In one embodiment internal pressure is measured to determine local stress. Different sensors may be employed to determine conditions for delivery of electrical therapy.

Additional programming modes are contemplated by the present description. For example, in one embodiment a variable programming mode incorporates traditional electrical pacing interspersed with specialized cell therapy pacing cycles.

In one embodiment, such pacing is used to provide complementary pacing therapies to a patient's heart to provide multiple benefits. In one embodiment, the varying pacing is applied using a duty-cycle approach. For example, a ratio of pacing of a first type to a pacing of a second type is programmed into the implantable device to provide a plurality of pacing therapies to a patient. This provides a new pacing mode where the programmability of duty cycle affords electrical therapy that complements at least one other pacing therapy and the administered cell therapy.

Another pacing variation provides a dynamically changing atrioventricular delay. In one exemplary embodiment, an atrioventricular delay is increased over a predetermined time period. For one example, an atrioventricular delay is lengthened by approximately one (1) millisecond each day over a predetermined time, such as three (3) months. In one embodiment, the atrioventricular delay is lengthened by 10 milliseconds over a predetermined amount of time, such as 2 months. In such embodiments, incremental increase in atrioventricular delay results in progressively loading a cardiac region, based on location of the electrodes. Similar but opposite effects might be obtained by progressively shortening the atrioventricular delay. Certain areas of the myocardium might be progressively unloaded, resulting in desired phenotypical changes at the chamber, tissue and cell levels.

Other embodiments and combinations are possible without departing from the scope of the present therapy system. The foregoing examples are intended to demonstrate some varying embodiments of the present therapy system, and are not intended in an exclusive or exhaustive sense.

In one embodiment, the pacing lead is positioned as close as possible to the site of engraftment. Positioning is performed using electrophysiology (e.g., ECG), echocardiographic mapping, or catheter based voltage mapping of the heart. Other location methods are possible without departing from the scope of the present teachings.

Lead placement is possible using epicardial leads implanted with minimal thorocotomy, and/or catheter leads. Treatment of the left ventricular region is possible using leads positioned in the coronary venous structures.

It is understood that a plurality of infarcted tissue regions may be treated using multiple cell and electrical therapy treatments.

Non-human animal models, e.g., rodent, lapine, canine or swine models, may be employed to determine pacing and cellular parameters useful to inhibit or treat a particular indication or condition. See, e.g., Jain et al., supra; Suzuki et al., supra; Pouleur et al., Eur. J. Clin. Investig., 13, 331 (1983); Hammond, J. Clin. Res., 92, 2644 (1993); Taylor et al., Proc. Assoc. Am. Phys., 109, 245 (1997); and Roth et al., J. Clin. Res., 91, 939 (1993)). For an animal model of MI, efficacious pacing and cell therapy results in improvement in cardiac function, e.g., increased maximum exercise capacity, contractile performance, and propagation velocity, decreased deleterious remodeling, decreased post-scar expansion, decreased apoptosis, increased angiogenesis, and increased donor cell engraftment, survival, proliferation, and function. Donor cell function can be determined using biochemical markers, e.g., myotube formation in grafted donor cells, the presence and/or levels of α-actinin, titin, myomesin, sarcomeric myosin heavy chain, α-actin and the like, and gap junction proteins (see Pimentel et al., Circulation Res, 90, 671 (2002)), as well as by improvements in global and regional cardiac function in recipients of donor cells. In *ex vivo* models, systolic and diastolic pressure-volume relations can be used to determine the efficacy of a particular therapy.

Example Cardiac Function Management Device

FIG. 3 shows a pacemaker performing the electrical therapy described herein. As used herein, the term pacemaker should be taken to mean any cardiac rhythm management device for pacing the heart and includes implantable pacemakers, external pacemakers, and implantable cardiac defibrillator/converters having a pacing functionality. A block diagram of a cardiac pacemaker having two ventricular pacing channels is shown in FIG. 3. Microprocessor 310 communicates with a memory 312 via a bidirectional data bus. In varying embodiments memory 312 comprises a ROM or RAM for program storage and a RAM for data storage. In one embodiment, the control unit includes dedicated circuitry either instead of, or in addition to, the

programmed microprocessor for controlling the operation of the device. In one embodiment, the pacemaker employs a programmable microprocessor to implement the logic and timing functions for operating the pacemaker in accordance with a specified pacing mode and pacing parameters as well as for performing the data acquisition functions. A telemetry interface 340 is also provided for communicating with an external programmer. Such an external programmer may be used to change the pacing mode, adjust operating parameters, receive data stored by the device, and issue commands that affect the operation of the pacemaker. Such an interface also provides communications with advanced patient management devices, such as portable computers, PDA's, and other wireless devices as described herein and provided by the documents incorporated herein.

In embodiments incorporating physical motion detection for application of therapy the pacemaker includes sensors to detect exercise. For example, accelerometers and minute ventilation sensors may be incorporated for these purposes. Some embodiments may incorporate time of day for application of therapy. Such embodiments may include timing modules and may update them using information from a programmer or other wireless device.

The pacemaker has atrial sensing/stimulation channels comprising electrode 334, lead 333, sensing amplifier/filter 331, pulse generator 332, and an atrial channel interface 330 which communicates bidirectionally with a port of microprocessor 310. The device also has two ventricular sensing/stimulation channels that include electrodes 324A-B, leads 323A-B, sensing amplifiers 321A-B, pulse generators 322A-B, and ventricular channel interfaces 320A-B where "A" designates one ventricular channel and "B" designates the other. For each channel, the same lead and electrode are used for both sensing (i.e., detecting P-waves and R-waves) and stimulation. The ventricular electrodes could be disposed in each of the ventricles for biventricular pacing or in only one ventricle for multi- site pacing of that ventricle. The channel interfaces 320A-B and 330 include analog-to-digital converters for digitizing sensing signal inputs from the sensing amplifiers and registers which can be written to by the microprocessor in order to output stimulation pulses, change the stimulation pulse

amplitude, and adjust the gain and threshold values for the sensing amplifiers. After digitization of the sensed signals by the channel interfaces, the signal samples can be processed in the digital domain by algorithms executed by the microprocessor in order perform further filtering. The detection of R wave and P wave peaks for timing purposes can also be performed digitally. Alternatively, a standard peak detection circuit could be used.

In one embodiment, the lead system includes endocardial leads, although other types of leads, such as epicardial leads, could also be used within the scope of the present teachings. In one embodiment, a first ventricular lead system is adapted for placement in a first cardiac region of the heart. In one example, the first cardiac region of the heart is within the coronary sinus and/or the great cardiac vein of the heart adjacent to the left ventricle. In one embodiment, the first lead system includes a number of electrodes and electrical contacts. A tip electrode is located at, or near, the distal end of the first lead system, and connects electrically to terminal through a conductor provided within the first lead system. The first lead system also includes a proximal electrode which is spaced proximal the tip electrode. In one embodiment, the proximal electrode is spaced proximal the tip electrode for placement adjacent to the left ventricle of the heart. The proximal electrode is electrically connected to terminal through an internal conductor within the first lead system. The proximal electrode can be of either an annular or a semi-annular construction, encircling or semi-encircling the peripheral surface of the first lead system.

The pacemaker further includes a second ventricular lead system. In one embodiment, the second lead system is an endocardial lead, although other types of leads, such as epicardial leads, could be used within the scope of the present teachings. The second ventricular lead system is adapted for placement within a second cardiac region of the heart. In one example, the second cardiac region of the heart is the right ventricle of the heart. In one embodiment, the second lead system includes a number of electrodes and electrical contacts. For example, in one embodiment, a tip electrode is located at, or near, the distal end of the second lead system, and connects electrically through a conductor provided in the lead, for connection to terminal. The

second lead system further optionally includes a first defibrillation coil electrode spaced proximal to the distal end for placement in the right ventricle. The first defibrillation coil electrode is electrically connected to both terminals and through internal conductors within the body of the second lead system. The second lead system also optionally includes a second defibrillation coil electrode, which is spaced apart and proximal from the distal end of the second lead system such that the second defibrillation coil electrode is positioned within the right atrium or major vein leading to the right atrium of the heart. The second defibrillation coil electrode is electrically connected to terminal through an internal conductor within the body of the second lead system.

In varying embodiments, the system includes multiple atrial electrodes and optionally includes the defibrillation components. The configuration and placement of electrodes may vary without departing from the scope of the present teachings.

In one embodiment, the pacemaker is a programmable microprocessor-based system, with a microprocessor and memory, which contains parameters for various pacing and sensing modes. Pacing modes include, but are not limited to, normal pacing, overdrive or burst pacing, and pacing for prevention of ventricular tachyarrhythmias. The system also includes means for adjusting atrioventricular delay. The microprocessor further includes means for communicating with an internal controller, in the form of an RF receiver/transmitter. This includes an antenna, whereby it may receive and transmit signals to and from an external controller. In this manner, programming commands or instructions can be transferred to the microprocessor after implant. In one embodiment operating data is stored in memory during operation. This data may be transferred to the external controller for medical analysis.

In one embodiment, pacing pulses are controlled by the microprocessor to carry out a coordinated pacing scheme at the two ventricular pacing locations. Pacing modes include, but are not limited to, normal sinus rhythm pacing modes, overdrive or burst pacing modes for treating ventricular tachyarrhythmia, and/or pacing regimens for preventing the onset of a ventricular tachyarrhythmia. Additional advantages for

providing pacing from the two ventricular pacing locations include the ability for either one of the two pacing systems to serve as a back-up pacing system and location for the other in the event that one pacing system were to fail.

Atrial sensing circuit is coupled by an atrial lead to a heart for receiving, sensing, and/or detecting electrical atrial heart signals. Such atrial heart signals include atrial activations (also referred to as atrial depolarizations or P-waves), which correspond to atrial contractions. Such atrial heart signals include normal atrial rhythms, and abnormal atrial rhythms including atrial tachyarrhythmias, such as atrial fibrillation, and other atrial activity. An atrial sensing circuit provides one or more signals to controller to indicate, among other things, the presence of sensed intrinsic atrial heart contractions.

An atrial therapy circuit provides atrial pacing therapy, as appropriate, to electrodes located at or near one of the atria of the heart for obtaining resulting evoked atrial depolarizations. In one embodiment, the atrial therapy circuit also provides cardioversion/defibrillation therapy, as appropriate, to electrodes located at or near one of the atria of the heart, for terminating atrial fibrillation and/or other atrial tachyarrhythmias.

Although FIG. 3 shows a human with an implanted cardiac rhythm management device, it is understood that the teachings may be used with devices other than cardiac rhythm management devices. The teachings are also applicable to non-mammalian heart therapies. Those skilled in the art, upon reading and understanding the present description, shall appreciate other uses and variations within the scope of the present teachings.

FIG. 4 shows one example of administration of cell therapy and electrical therapy to a region of cardiac tissue subject to myocardial infarction. The heart 402 includes a left ventricle 404 which has tissue injured by a myocardial infarction 400. The affected region 400 is determined by methods including those described herein. Cell therapy 406 is preferably administered in close proximity to, e.g., transvenously, transarterially, intramyocardially or in adjacent non-infarcted tissue, and/or directly to

the affected region 400 and electrical therapy is applied using a programmable pulse generator 408 and lead 410.

The electrical therapy includes pacing *in vivo* preferably near infracted or hybernating myocardium and including sites targeted for cell therapy to enhance the engraftment, survival, proliferation, and/or function, and optionally the differentiation, of the cells. The pacing may be applied to lessen local stress and strain that might otherwise inhibit the successful engraftment of donor cells including the successful formation of gap junctions between donor cells and noninfarcted recipient myocardial cells. Such therapy thus affects both mechanical and electrical connections to neighboring cells of the native myocardium. In particular, pacing at or near such sites may enhance development of new gap junctions which may be needed for coordinating the function of the donor cells with that of the native myocardium. The therapy also operates to control metabolic demands at the site of targeted cell therapy to increase donor cell viability. Another benefit is that electrical stimulation of myocytes promotes release of factors that encourage angiogenesis. In one embodiment, preconditioning of cells cultured *in vitro*, e.g., with drugs or other chemical agents, and/or transgene expression, and/or electrical stimulation and/or mechanical stimulation, may benefit *in vivo* engraftment, survival, proliferation, differentiation and/or functioning of the cells.

In vivo left ventricle pacing controls local stress by managing atrioventricular delay, RV-LV offset, stimulation site alternation, heart rate, and pacing waveform parameters. The LV stimulus also promotes donor cell engraftment, survival, proliferation, differentiation and/or functioning *in vivo* and is controllable based on pacing waveform, rate, and site.

In one embodiment, the pacemaker is programmed to perform VDD pacing using an atrioventricular delay which is relatively short when compared to the intrinsic atrioventricular interval. Other electrical therapies are possible given the teachings herein. For example, it is possible that the affected region is pre-treated to strengthen the region before injection of cell therapy. Upon reading and understanding the

teachings provided herein, those skilled in the art will understand other electrical therapies are possible without departing from the scope of the present teachings.

FIG. 5A is a schematic drawing illustrating, by way of example, but not by way of limitation, one embodiment of portions of a cardiac rhythm management system 500 and an environment in which it is used. System 500 includes an implantable cardiac rhythm management device 505, also referred to as an electronics unit, which is coupled by an intravascular endocardial lead 510, or other lead, to a heart 515 of patient 520. System 500 also includes an external programmer 525 providing wireless communication with device 505 using a telemetry device 530. Catheter lead 510 includes a proximal end 535, which is coupled to device 505, and a distal end 540, which is coupled to one or more portions of heart 515. Although FIG. 5A shows a human with an implanted cardiac rhythm management device, it is understood that the teachings may be used with devices other than cardiac rhythm management devices. The teachings are also applicable to non-mammalian heart therapies. Those skilled in the art, upon reading and understanding the present description, shall appreciate other uses and variations within the scope of the present teachings.

FIG. 5B is a diagram showing a wireless device in communications with an implanted device for management of the implanted device and therapy according to one embodiment of the present invention. In one embodiment, wireless device 555 is used to conduct communications with pacemaker 505. In one application, wireless device 555 is a personal digital assistant (PDA). In one embodiment, wireless device 555 is a computer with wireless interface. In one embodiment, wireless device 555 is a cellular phone. The communications between pacemaker 505 and wireless device 555 can be used for coordinating operations and therapies of the pacemaker and/or to communicate device operations and physiological data to another site in communications with the wireless device 555. FIG. 5C shows one example of communications where a network 565 is in contact with wireless device 555. The connection between wireless device 555 and network 565 can be either wired or wireless. In one embodiment, network 565 is the Internet. Remote facility 575 is a

medical facility or location which a doctor or health care provider can access data from the pacemaker 505. Alternatively, data and/or instructions can be transmitted from the remote facility 575 to the wireless device 555 and/or the pacemaker 505. Alternatively, instructions and data can be transferred bidirectionally between the remote facility, wireless device, and/or pacemaker 505.

The network is a communication system that interconnects a number of computer processing units when those units are some distance away from one another, but within the same contiguous property to allow private communications facilities to be installed. The network may also include the facility to allow multiple compute processors to communicate with each other when some or all of those processors are within the same enclosure and connected by a common back plane.

Connections with a remote facility and wireless device are useful for advanced patient management. Some exemplary apparatus and methods for patient management include, but are not limited to, the teachings provided in the patent application entitled: Method and Apparatus for Establishing Context Among Events and Optimizing Implanted Medical Device Performance, U.S. Ser. No. 10/093353 filed March 6, 2002, which is incorporated by reference in its entirety.

Combined Cell and Electrical Therapy Example

In one embodiment, skeletal muscle cells are obtained from a patient who recently, e.g., within the previous 1 to 7 days, suffered a myocardial infarction. The skeletal muscle cells may be cultured *in vitro*, e.g., so as to expand the population, or may be employed in the absence of culturing. Prior to cell therapy, the damaged tissue in the patient is located by conventional means, e.g., an electrocardiogram. The autologous donor skeletal muscle cells, prior to administration to the damaged tissue, may be optionally subjected to washing to remove non-cellular components, i.e., components which are not intact cells including components in tissue culture media, and introduced to the damaged tissue in a physiologically compatible carrier (vehicle), e.g., an aqueous, semi-solid or solid vehicle. In one embodiment, approximately 10^2 to 10^{10} donor skeletal muscle cells are administered via a catheter, which includes an

injection needle, plurality of needles, or infusion port, positioned at or near the damaged tissue. A biocompatible (e.g., biodegradable) marker may be administered with the skeletal muscle cells so as to monitor the site(s) of administration of the donor cells and, optionally, later identify the treated region. Once administered, the donor cells develop functional connections with adjacent viable cells, and membrane channels with adjacent viable cells.

In one embodiment, the area including the damaged tissue and donor cells in the patient are then subjected to electric conditioning, such as pacing-level electrical stimulation, using a pulse generator with properly positioned electrodes, which in combination with cell therapy results in an improvement in global and regional cardiac function in the patient. A pacing regimen is provided where the pacemaker is programmed to perform VDD pacing using an atrioventricular delay which is relatively short when compared to the intrinsic atrioventricular interval.

In General

Although the present therapy is described in the example of cardiac therapy, it is understood that many other applications are possible. Such teachings may be applied to *in vitro* and *in vivo* treatment of other organs and blood vessel growth.

It is to be understood that the above description is intended to be illustrative, and not restrictive. Other embodiments will be apparent to those of skill in the art upon reviewing and understanding the above description. The scope of the invention should, therefore, be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.